Appendix

Infectious causes of microcephaly: Epidemiology, Pathogenesis, Diagnosis, and Management


Citation: Devakumar D, Bamford A, Ferreira MU, et al. Infectious causes of microcephaly: epidemiology, pathogenesis, diagnosis, and management. *Lancet Infect Dis* 2017; published online Aug 22. [http://dx.doi.org/10.1016/S1473-3099(17)30398-5](http://dx.doi.org/10.1016/S1473-3099(17)30398-5)


Supplementary Table 1. Clinical features of the major congenital infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>CMV</th>
<th>HSV</th>
<th>Rubella</th>
<th>T. gondii</th>
<th>ZIKV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>12·7% symptomatic at birth</td>
<td>40-58% long term sequelae</td>
<td>Only 5% of cases of neonatal HSV are attributable to <em>in utero</em> transmission</td>
<td>24% of live born infected infants symptomatic at birth</td>
<td>Congenital infection estimated as 29% in a preliminary analysis of a cohort in Brazil</td>
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<tr>
<td>Microcephaly</td>
<td>35% of symptomatic children with congenital CMV identified through screening</td>
<td>16% of cases of <em>in utero</em> transmission</td>
<td>27-42% of congenital rubella syndrome</td>
<td>5-10% of symptomatic cases</td>
<td>Currently uncertain risk. Modelling based on data from French Polynesia estimated a risk of 1% (95% CI 0·3, 1·9%) infected the first trimester developed microcephaly.</td>
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</table>

Notes:
1. [http://dx.doi.org/10.1016/S1473-3099(17)30398-5](http://dx.doi.org/10.1016/S1473-3099(17)30398-5)
<p>| Central nervous system findings | 71% of symptomatic children identified through screening CT abnormal and 48% had calcification. Lissencephaly and polygyria also reported. | Calcification in up to 30% of cases of <em>in utero</em> transmission. Other structural abnormalities including porencephaly, ventriculomegaly also described. Evidence from case series: subcortical anterior temporal cysts, periventricular and basal ganglia calcification and white matter hyperintensities in the periventricular and subcortical regions. | 13% intracranial abnormality (calcification, ventricular dilatation), higher rates the earlier infection occurs in pregnancy. Case studies of 23 infants with microcephaly show that all had calcifications in the cortical-subcortical junction and a range of other malformations including cortical gyral abnormalities (pachygyria, polymicrogyria and lissencephaly), brain stem abnormalities, ventriculomegaly, and myelination changes. | 3-4% of live births from a prospective cohort in Brazil. Low risk in the second and third trimesters. |
| Skin and musculoskeletal | Petechiae 55%, purpura 3% of symptomatic children identified through screening | 95% of cases of <em>in utero</em> transmission have skin lesions, 17% have limb and bone abnormalities. Purpura 17% | Up to 25% have a rash. Skin findings may include petechiae, ecchymoses, purpura, and blue-red &quot;blueberry muffin&quot; lesions. Arthrogryposis No skin lesions reported but excessive scalp skin noted | |
| Eyes | Visual impairment 22-58% of symptomatic children identified through screening | 39% of cases of <em>in utero</em> transmission have ophthalmologic abnormalities. 78% ocular involvement (pigmentary retinopathy, cataracts, microphthalmia) 86% visual loss 25% cataracts, 5% retinopathy | 18% ocular involvement (retinochoroiditis, microphthalmia). Can develop as a late manifestation throughout childhood and adolescence. A study of 29 infants with microcephaly showed ocular abnormalities were present in 35%: focal pigment mottling of the retina and chorioretinal atrophy, optic nerve abnormalities, iris |</p>
<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
<th>Data Source</th>
<th>Notation or Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematology</td>
<td>Thrombocytopenia 38% of symptomatic children identified through screening</td>
<td>No data available</td>
<td>Thrombocytopenia reported to occur</td>
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<tr>
<td>Neurodisability</td>
<td>Cognitive defects 35% of symptomatic</td>
<td>Minimal data. High rate of developmental delay when reported in surviving children 8</td>
<td>62% psychomotor retardation 13-41% mental retardation 8 11</td>
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<td></td>
<td>Neurological sequelae (inc SNHL in 35-45% symptomatic) 6·5% of asymptomatic develop cognitive/ neurological impairment 1 25% IQ &lt;70, 16% motor deficit in symptomatic children identified through screening 7 Normal development at 1 year predicts normal neurological outcome 30,31</td>
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<td>Hearing loss</td>
<td>SNHL 35% of symptomatic, 36% of symptomatic through screening 2,7 SNHL in 7-10% asymptomatic 2 In developed countries 21% SNHL at birth, 24% at 4 years.</td>
<td>Rare reports of SNHL 35</td>
<td>Hearing loss is common in congenital rubella syndrome and is the most common single defect. Estimates range from 60-95% 9-11</td>
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<td>Cardiac</td>
<td>Not commonly reported</td>
<td>Not commonly reported</td>
<td>Estimates vary from 45-66%, Main cardiac defects are patent ductus arteriosus and pulmonary stenosis 9-11</td>
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</table>
Liver

- Jaundice in 40%, hepatosplenomegally in 17%, Transaminitis 55% of symptomatic children identified through screening.

- 28% of cases of in utero transmission have liver impairment.

- Hepatosplenomegaly 19%.

- Can lead to hepatomegaly and cholestatic jaundice and occasionally liver calcifications.

- Hepatomegaly not reported.

Death

- 4% of symptomatic cases.
- 0-5% of all infections identified through screening.

- 45% of cases of in utero transmission.

- 3-4% if infected in the first trimester.

- Rare in modern case series – mainly therapeutic termination (<2%) 5,33

- Unknown but fetal deaths have been reported. 38,39

SNHL: Sensorineural hearing loss

References


